DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 343

[Docket No. 77N–094A]

RIN 0910–AA01

Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-The-Counter Human Use; Final Rule for Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination With Antacid Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing as a final rule professional labeling for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic drug products containing aspirin, buffered aspirin, and aspirin in combination with an antacid. This portion of the final monograph is being issued prior to the entire monograph so that the professional labeling of these products will reflect the latest information on cardiovascular, cerebrovascular, and rheumatologic uses. FDA is issuing this final rule after considering comments on the agency's proposed regulation for OTC internal analgesic, antipyretic, and antirheumatic drug products, a proposed amendment to the regulation, and data and information that have come to the agency's attention.

EFFECTIVE DATE: (*Insert date 12 months after date of publication in the* **Federal Register**.)

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 16, 1988 (53 FR 46204), FDA published, under 21 CFR 330.10(a)(7), a notice of proposed rulemaking, in the form of a tentative final monograph (TFM), that would establish conditions in part 343 (21 CFR part 343) under which OTC internal analgesic, antipyretic, and antirheumatic drug products are generally recognized as safe and effective and not misbranded. In the TFM (53 FR 46204 at 46258 and 46259), the agency proposed professional labeling in § 343.80 for the use of aspirin for rheumatologic diseases, for reducing the risk of recurrent transient ischemic attacks (TIA's) or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli, and for reducing the risk of death and/or nonfatal myocardial infarction (MI) in patients with a previous infarction or unstable angina pectoris. The agency also proposed professional labeling for the use of carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate for rheumatologic diseases. Interested persons were invited to submit new data or file written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal.

In response to the TFM, the agency received four comments and three citizen petitions related to the professional labeling of aspirin for cardiovascular and cerebrovascular uses (Ref. 1). No comments were received on the professional use of aspirin drug products for rheumatologic diseases. In response to two of the petitions, the agency proposed to amend the professional labeling section of the TFM for OTC internal analgesic, antipyretic, and antirheumatic drug products to include an indication for aspirin for suspected acute MI (61 FR 30002, June 13, 1996). In response to the proposed amendment, the agency received 10 comments (Ref. 2).

In the TFM for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46204 at 46205), and in the proposed amendment to the TFM (61 FR 30002), the agency proposed that any final rule that may issue based on the proposal will be effective 12 months after the date of publication in the **Federal Register**. Therefore, on or after (*insert date 12 months after*

date of publication in the **Federal Register**), the dissemination of professional labeling that does not comply with this final rule may result in regulatory action against the product, the marketer, or both. Manufacturers are encouraged to comply voluntarily with this final rule at the earliest possible date.

The labeling in this final rule for professional use of aspirin drug products contains complete information on certain professional uses of aspirin, including information for professionals on the treatment of the signs and symptoms of rheumatologic disease. The labeling is organized and presented in a manner similar to that required of prescription drug products under §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57). The labeling in this final rule also includes an optional highlights section that summarizes the professional indications and the recommended dosage and administration for each professional indication.

II. The Agency's Conclusions on the Comments

A. Comments to the TFM

1. One comment requested that aspirin be approved for use as a prophylaxis for primary (first) MI under a physician's supervision. The comment based its request on the preliminary report of a large, highly statistically significant, reduction (47 percent) in the risk of total (fatal and nonfatal) MI in subjects taking aspirin in the U.S. Physicians' Health Study (Ref. 3). A final report was published later (Ref. 4).

The agency also considered the British Doctors Study, by Peto et al. (Ref. 5), that was similar in many respects to the U.S. Physicians' Health Study. It randomized 5,139 apparently healthy male doctors, to 500 milligrams (mg) aspirin daily, or to no aspirin, to see whether aspirin would reduce the incidence of, and mortality from, stroke, MI, or other vascular conditions. The British Doctors Study, despite its similarity to the U.S. Physicians' Health Study, does not support the use of aspirin to prevent an initial MI. After 6 years of followup, there were 23.5 confirmed nonfatal MI reports per 1,000 participants in the aspirin group and 24 per 1,000 in the no-aspirin group.

When possible MI reports were added, the total was 30 per 1,000 for the aspirin group and 26.4 per 1,000 for the no-aspirin group. From a safety viewpoint, disabling stroke was significantly more frequent in the aspirin group than the no-aspirin group (19.1 versus 7.4 per 10,000 man years, $p < 0.05$). In addition, expected gastrointestinal (GI) events (e.g., nonfatal peptic ulcers, bleeding, dyspepsia) occurred in the aspirin group.

On October 6, 1989, FDA's Cardiovascular and Renal Drugs Advisory Committee (the Committee) considered a claim for aspirin for the prevention of primary (first) heart attack based on the findings of the U.S. Physicians' Health Study (Refs. 3 and 4). The Committee was aware of the findings of the British Doctors Study, but only the findings from the U.S. Physicians' Health Study were presented in detail. The Committee recommended (by a 5 to 3 vote) that, although some claim should be considered for some high-risk group of patients, aspirin should not be used routinely in patients without risk factors or in women, until such patients had been studied. The Committee minority was concerned about the toxicity of aspirin and the number of normal individuals at low risk of having a heart attack who would be treated long term. The Committee unanimously agreed that patients should ask their doctor before beginning prophylactic therapy. The agency has considered the Committee's views in conjunction with the additional data that have been subsequently submitted to FDA.

The agency does not consider the results of the aspirin component of the U.S. Physicians' Health Study adequate to support the effectiveness of aspirin in decreasing the risk of MI in healthy individuals without evidence of coronary artery disease because of concerns about the revised primary endpoint, the study population, and the results of the British Doctors Study.

The primary endpoint described in the protocol for the aspirin component of the U.S. Physicians' Health Study was total cardiovascular mortality. On interim evaluations, however, it became clear to the Data Monitoring Board (DMB) for the study that the aspirin arm of the study had little chance of showing a survival effect before the year 2000, if then, because the mortality rate was far lower than expected and the study did not show even a positive trend for this endpoint.

There were 81 deaths in the aspirin group and 83 in the placebo group ($p = 0.87$). The DMB also took note of the reductions in total (fatal and nonfatal) MI, a finding they considered persuasive. Because the study had little hope of showing an effect on the primary endpoint and because of the reduction in MI, the DMB recommended early termination of the aspirin component of the trial (Ref. 3). The early stopping rule stated in the grant proposal (but not in the protocol) was that the trial would continue unless chi-square tests comparing treatments reached an extreme value, such as 9.0 (i.e., if $p < 0.0027$). The proposal did not state explicitly which endpoint was the basis for the early stopping rule. It is not clear which endpoint served as the basis for the early stopping rule. Thus, it is not clear how the reported p values should be adjusted retrospectively although some adjustment would be required.

The finding of a reduction in risk of MI in the U.S. Physicians' Health Study is further weakened because some of the study patients had a prior MI, and aspirin is already known to reduce the risk of recurrent MI in such patients. According to the study protocol, subjects should not have had an MI before randomization. However, based on the agency's inspection of the subjects' records, at least 40 (about 8 percent) of the 512 subjects who suffered a nonfatal MI during the study also had evidence of an old MI. The exact number of cases with prior MI in the entire study population at the time of randomization is not known. Therefore, it is not possible to determine with assurance how much of the effect of aspirin attributed to prevention of a primary MI was really prevention of a reinfarction.

The U.S. Physicians' Health Study also found a statistically significant reduction in the risk of fatal acute MI in the aspirin group, but no overall effect on survival. The agency does not consider this finding persuasive. Assessing cause-specific mortality is usually difficult and the finding of benefit is of uncertain meaning in the face of equivalent total cardiovascular mortality (the original primary endpoint). Thus, the decrease in acute MI deaths in the aspirin group were almost matched by an increase in sudden deaths, not an obviously worthwhile effect. Redefinition of endpoints would, in any case, require adjustment for multiplicity, but it is difficult to describe

the appropriate adjustment, as the number of possible secondary endpoints is unspecified. The nominally significant decrease of fatal MI ($p = 0.004$) thus needs considerable upward adjustment and would not be close to the significance level needed at an interim point ($p < 0.0027$).

In addition, some of the cause of death assignments are questionable. The agency evaluated the deaths in the study attributed to fatal acute MI (10 in the aspirin group and 28 in the placebo group) and to "sudden death" (22 in the aspirin group and 12 in the placebo group) and found that one death in the placebo group attributed to acute MI was due to stroke. Another placebo subject classified as MI had no evidence of MI, but could have been classified as a "sudden death." Thus the number of confirmed MI's in the placebo group decreases from 28 to 26, and the number of "sudden deaths" increases from 12 to 13.

On the other hand, the autopsy report of one aspirin subject categorized under "sudden death" listed acute MI as the cause of death. Another aspirin subject, in the sudden death category, experienced chest pain and vomiting before collapsing, and the autopsy showed "moderate to severe 3-vessel atherosclerosis with apparent myocardial ischemia in a patient with right and left myocardial hypertension and extensive old septal scarring." It is likely that this patient's death was due to acute MI. Thus, if 2 of the 22 deaths in the aspirin group classified as "sudden death" had been classified as confirmed acute MI (increasing that total from 10 to 12), the "sudden death" total would be decreased from 22 to 20. The cause of death could not be established with certainty in most subjects. All subjects in the "sudden death" category for whom relevant information was available had a history of atherosclerotic cardiovascular disease, peripheral vascular disease, or hypertension. Therefore, all of the cases of sudden death could have resulted from an acute MI. Thus, there could have been 32 cases (12 identified, 20 possible) of fatal MI in the aspirin group versus 39 (26 identified, 13 possible) in the placebo group. This difference is not statistically significant ($p > 0.50$). This analysis could be considered a "worst case" analysis of the fatal MI finding, but it illustrates the difficulty of cause-specific mortality findings.

The agency also does not believe the reported 18 percent reduction in the endpoint of nonfatal MI, nonfatal stroke, and total cardiovascular mortality can be taken as significant. For the combined endpoint, there were 307 subjects in the aspirin group and 370 in the placebo group (relative risk 0.82; p = 0.01). The reported p value of 0.01 is well above the stopping rule p value of 0.0027. Therefore, the study did not provide persuasive evidence that aspirin has a beneficial effect on the combined endpoint. In addition, the isolated finding of a statistically significant effect on nonfatal MI is not persuasive. Of note is the fact that the British Doctors Study completely failed to replicate this finding.

The reduction in incidence of fatal and nonfatal MI was also accompanied by an increase in strokes, especially severe, fatal, hemorrhagic stroke, and by a greater incidence of sudden death and "other" cardiovascular deaths. Thus, there was no overall benefit or favorable trend on mortality. Cerebral hemorrhage as a cause of stroke was reported more often in the aspirin group than in the placebo group (23 versus 12). The incidence of ulcers, "other noninfectious diseases of the digestive tract," bleeding problems, and the need for transfusion, also was significantly increased, and one aspirin subject died from GI bleeding. Although these side effects would not prevent the use of aspirin if its net benefit on coronary artery and cerebrovascular events were favorable, the effects are not trivial.

It seems probable that the net benefit of aspirin is critically dependent on the underlying risk for coronary and cerebral events, and that use of aspirin requires knowing more about its effects in various populations. In people at low risk for acute MI, the increased risk of stroke may result in a net disadvantage. In at least some people at higher risk (people who have had an acute MI or have TIA's), aspirin is known to provide a net benefit. There may be other populations in whom the net effect of aspirin is favorable, but the U.S. Physicians' Health Study does not define such groups. The investigators did not identify any group in which aspirin could reduce the incidence of fatal and nonfatal heart attack without increasing the incidence of other causes of death or disability.

The Steering Committee of the U.S. Physicians' Health Study Research Group (Ref. 4) suggested that aspirin is beneficial in prevention of the first heart attack (at least in men over 50), but stated: "Although the short-term benefit of aspirin in these populations appears to outweigh its risks, the long-term advantage and toxicity of the drug remain uncertain." In a more recent review article (Ref. 6) by several members of the U.S. Physicians' Health Study Research Group, members of the Steering Committee, and others, concerning primary prevention of MI, the authors concluded the following: "Any decision to use aspirin prophylaxis should be made on an individual basis and, in general, should be considered only for those whose absolute risk of a first MI is sufficiently high to warrant accepting the potential adverse effects of long-term aspirin use."

In summary, the U.S. Physicians' Health Study failed to show a significant effect, or even a beneficial trend, on the specified primary study endpoint of total cardiovascular mortality. The study was stopped early and multiple secondary endpoints were evaluated. The effects of aspirin on fatal acute MI and on the combined endpoint of nonfatal MI, nonfatal stroke, and total cardiovascular mortality were not statistically significant when adjustments were made for early stopping. There was an isolated finding of a statistically significant effect on nonfatal MI (a secondary endpoint), but the value of this finding is questionable in the face of adverse trends on stroke and causes of death other than acute MI. Of note is the fact that the British Doctors Study completely failed to replicate this finding on nonfatal MI. Thus, the agency concludes that the available data do not support the professional labeling of aspirin for the prevention of first MI. The U.S. Physicians' Health Study (Refs. 3 and 4), in particular, did not show a statistically significant effect when all deaths as well as nonfatal MI and stroke were combined.

2. One comment asked that the professional labeling in proposed § 343.80(b) for aspirin for TIA include both men and women, not just men. The comment cited results from the Second International Study of Infarct Survival (ISIS–2) (Ref. 7), based on an analysis of a subset of data for men and women separately, to support its request. The absolute decrease in mortality for the aspirin group compared to placebo was 2.4 percent for men and 2.6 percent for women. The

comment concluded that this study showed that, up to 5 weeks, mortality was significantly reduced ($p < 0.01$) in both men and women who had suffered acute MI and were treated for 1 month with aspirin. The comment added that this study also showed that aspirin reduced the incidence of nonfatal stroke and nonfatal MI in both men and women.

The comment complained that the study (Ref. 8) supporting the use of aspirin only in men to reduce the risk of recurrent TIA or stroke was only one small trial with a marginally significant overall result. The comment mentioned that the results of this study were subdivided by gender, and a data-dependent subgroup analysis suggested an effect only in men. Such subgroup analysis, the comment contended, is frequently unreliable. The comment suggested that the ISIS–2 study results, which showed reduced mortality in both men and women given aspirin following acute MI, should ''illuminate'' data from trials in a different occlusive vascular disease (TIA).

The agency is in substantial agreement with the comment that there is no reason to distinguish between genders with respect to using aspirin to reduce the risk of recurrent TIA or stroke. Although subset differences are known to occur, in general, results are considered applicable to the whole group unless there is reason not to do so (Ref. 9). In the present case there was, initially, reason to limit the TIA claim to males. The indication in proposed § 343.80(b) was based on results of the Canadian Cooperative Study Group trial (Ref. 8) and the Fields study (Ref. 10). In these studies, there seemed to be a difference in response with gender when subset analyses were done. However, there were very few women in the trials and the number of events reported was small.

Data from subsequent trials do not substantiate a gender difference in the effect of aspirin on cerebrovascular events, and trends in women have been similar to results seen in men. The UK–TIA aspirin trial (Ref. 11), in which 25 percent of the subjects were women, showed favorable trends for the endpoint of major stroke, MI, or death. The AICLA study (Ref. 12), which reportedly showed an effect of aspirin for secondary cerebral events in a group that included 30 percent women, showed no significant difference between men and women. Although the study was small, subset analysis showed a trend favoring women, with a numerically larger effect on stroke in

women than in men. The study by Sivenius et al. (Ref. 13) included a larger proportion of women (42 percent in the intent-to-treat analysis and 44 percent in the explanatory analysis), and the investigators reported a statistically significant effect in women. That study did not include an aspirin-only arm, but there is little evidence that dipyridamole contributes to the effect of the aspirin plus dipyridamole combination (Refs. 12 and 14); thus, this study provides some support for an effect of aspirin in women. The Swedish Cooperative study (Ref. 15) failed to show an effect for aspirin overall, in men or in women.

The agency believes the available data support the conclusion that women with a history of TIA should benefit from aspirin therapy. Early evidence supporting this use of aspirin came from studies that included mostly men, but studies since the Canadian and Fields studies show numerically similar results for men and women. Favorable trends have generally been seen in women as well as men. Therefore, the agency is revising the professional labeling in § 343.80 for cerebrovascular uses so that the indication is for ''patients'' rather than for ''men.''

3. One comment asked that the dosage for aspirin for TIA in proposed § 343.80(b) be reduced from 1,300 mg to 300 mg a day. The comment contended that data from many different trials of antiplatelet treatments in many different occlusive vascular conditions could be viewed together. The comment stated that this approach could be used because, no matter what the prior medical condition may have been, the chief diseases to be prevented (occlusive stroke and coronary artery occlusion) may be much the same. The comment explained that aspirin doses of only 100 to 200 mg daily inhibit cyclo-oxygenase-dependent platelet aggregation so completely that little extra effect would result from higher daily doses. The comment cited the ISIS–2 study (Ref. 7) as showing that 160 mg aspirin daily was highly protective in preventing death ($p < 0.01$) and in reducing nonfatal stroke and nonfatal MI in subjects who suffered an acute MI.

The comment also cited the Trialists' report (Ref. 16), a meta-analysis of the results of 25 randomized clinical trials of the prolonged treatment with drugs that inhibit platelet aggregation. The comment stated that when the trials are viewed together: (1) The benefits of antiplatelet

treatment are about the same in cardiac patients (unstable angina and MI) as in cerebral patients (TIA and stroke thought to be occlusive), and (2) the various treatments used, including 300 mg of aspirin daily, were comparable. The comment mentioned that aspirin gastrotoxicity is dose-related, and cited the UK–TIA trial (Ref. 11) in which more GI symptoms (indigestion, nausea, heartburn, or vomiting) occurred with 1,200 mg than 300 mg daily aspirin (a difference of 9.4 percent ($2p < 0.001$)).

Another comment asked the agency to consider lower doses of aspirin for maintenance therapy. The comment described several serious nasal hemorrhages that occurred when taking maintenance therapy of "one half aspirin tablet (strength not stated) daily." The comment also mentioned a number of instances of sustained bleeding from shaving nicks, bleeding after accidents, bleeding ulcers, and complications during surgery based on personal experience or the experiences of friends or neighbors who were taking aspirin for maintenance therapy. The comment concluded that the proposed FDA dosage is several times the dosage needed for most maintenance therapy and that FDA should lower the dosage.

The agency has considered the dosage of aspirin for cardiovascular and cerebrovascular conditions and concludes that specific doses for specific uses of aspirin, supported by appropriate data, are necessary for an optimum benefit to the user, and, in general, that a minimum effective dose established for a given indication should be used to minimize dose-related adverse effects. The agency has determined that the ISIS–2 study (Ref. 7) supports the professional labeling of aspirin in the treatment of suspected acute MI at a dosage of 160 to 162.5 mg daily. However, the ISIS–2 study did not show, nor was it intended to show, the effect of aspirin on subjects with TIA or other cerebrovascular events.

The Trialists' report (Ref. 16) evaluated antiplatelet treatment of subjects with a range of symptoms (e.g., TIA, occlusive stroke, unstable angina, and MI) using a number of antiplatelet agents, not only aspirin. Some of the studies (Refs. 8, 10 through 12, 15, and 17 through 19) used aspirin alone and included cerebrovascular subjects given dosages ranging from 990 to 1,500

mg daily, except one arm of the UK–TIA study that used a dosage of 300 mg daily in parallel with a 1,200 mg dose. The primary endpoints of most of these studies were combined events, including strokes (fatal and nonfatal) and death. In some of the studies, TIA or MI was also included in the primary endpoint. The Trialists' group (Ref. 16) did a meta-analysis suggesting the effectiveness of lower doses of aspirin (less than 160 to 324 mg per day) in reducing combined events (nonfatal stroke, MI, or vascular death), but all studies except the UK–TIA study involved subjects with a history of MI or angina rather than a history of cerebrovascular events.

In a subsequent publication (Ref. 20), the Trialists' group provided some support for the role of antiplatelet therapy in prevention of nonfatal strokes in subjects with prior stroke or TIA. Among the 10 trials that used aspirin alone, dosages ranged from 50 to 1,300 mg per day. Three of these trials (UK–TIA, Danish Very-Low-Dose, and Swedish Aspirin Low-Dose Trial (SALT)) used comparatively low doses of aspirin (Refs. 11, 21, and 22).

The UK–TIA study (Ref. 11) alone showed no difference in effectiveness between the 300 mg and the 1,200 mg aspirin daily dose in a TIA population, but the incidence of side effects, especially GI, was greater for the 1,200 mg dose. The beneficial effect of aspirin on major stroke alone and on the composite events, disabling stroke or vascular death, was not sufficient to show a significant difference between aspirin and placebo, but it did show a trend in favor of aspirin. For the combined endpoint of all death, nonfatal major stroke, and nonfatal MI, the study showed an 18-percent (95 percent confidence interval, 2 to 31 percent) reduction by aspirin (combined 300 and 1,200 mg groups). The Danish Very-Low-Dose Study (Ref. 21) used aspirin doses ranging from 50 to 100 mg per day in subjects with TIA, stroke, or acute MI who had recently undergone carotid endarterectomies. The study showed no significant effect of aspirin and side effects were minimal. In the SALT study (Ref. 22), 75 mg aspirin daily reduced the risk of stroke and death by 18 percent in subjects who previously had TIA, minor ischemic stroke, or retinal artery occlusion. The agency also considered the findings of the second European Stroke Prevention Study (ESPS–2) (Ref. 23) in which 50 mg daily aspirin had a significant beneficial effect on the combined

risk of stroke or death in subjects with a prior TIA or ischemic stroke. (See section II.A, comment 4 of this document.)

The proposed indication for aspirin to reduce the risk of recurrent TIA or stroke in subjects with TIA, at a dosage of 1,300 mg daily, was based primarily on two small studies (Refs. 8 and 10). Other, more recently published studies (Refs. 11, 12, 22, and 23) have shown a significant effect or trend in favor of aspirin in a population with cerebrovascular events. The agency has reevaluated the available studies and the overall outcome of the available studies, looking at the role of aspirin on the endpoint of stroke alone and the broader composite endpoint of stroke and death, both individually and collectively. (See section II.A, comment 4 of this document.)

Although there is more evidence for effectiveness of aspirin for subjects with TIA or cerebral ischemia at higher doses (900 to 1,500 mg daily) than at lower doses (Ref. 24), the ESPS–2 (50 mg daily aspirin) (Ref. 23), the SALT study (75 mg aspirin daily) (Ref. 22), and UK–TIA study (300 mg versus 1,200 mg aspirin daily) (Ref. 11), lend support for a lower dose. Certain adverse reactions, such as excessive bleeding described by one of the comments, occur in some individuals taking aspirin, but there are generally fewer such reactions at lower doses than higher doses. This is supported by the UK–TIA study (Ref. 12). The benefit/risk must be taken into account for each indication. In this regard, the agency proposed a warning in § 343.50(c)(1)(v)(B) of the TFM to alert people who have bleeding problems not to take aspirin unless directed by a doctor (53 FR 46204 at 46256). Also, the professional labeling in this final rule lists GI bleeding in the adverse reactions section and notes that many adverse reactions due to aspirin ingestion are dose related.

In summary, there is clinical trial support for a lower dose of aspirin for subjects with a history of TIA or cerebral ischemia and considerable evidence supporting lower doses in patients with MI. It is also clear that the effect of aspirin on platelet function is complete at lower doses. The positive findings at lower dosages (e.g., 50, 75, and 300 mg daily), along with the higher incidence of side effects expected at the higher dosage (e.g., 1,300 mg daily), are sufficient reason to lower the dosage of aspirin for subjects with TIA and ischemic stroke. The agency believes

a dose of 50 to 325 mg is an effective daily dose for subjects with TIA or cerebral ischemia. Therefore, in this final rule, the agency is providing for a dosage of 50 to 325 mg aspirin daily.

4. One comment suggested the following indication for low-dose aspirin: ''For reduction of the risk of MI, stroke, and vascular death among men or women with a history of occlusive cerebral vascular or cardiovascular disease. The optimal dose is not known, but there is no good evidence that doses above 300 mg/day are necessary.''

The agency reviewed a number of published reports (individually and collectively) to further evaluate the effects of aspirin in subjects with premonitory cerebrovascular events. The agency evaluated studies that: (1) Compared aspirin alone to placebo in subjects with a history of cerebrovascular events, and (2) evaluated and adequately presented the endpoint of stroke and the composite endpoint of stroke and death. The agency considered reviews by the Antiplatelet Trialists' group (Refs. 16 and 20) and Matchar et al. (Ref. 24), but did not include combination arms (e.g., aspirin and dipyridamole) and studies of post-endarterectomy subjects (e.g., Danish Very-Low-Dose Study) (Ref. 21). The following studies met the criteria: SALT (Ref. 22), AICLA (Ref. 12), Canadian Cooperative (Ref. 8), AITIA (Ref. 10), Danish Cooperative (Ref. 18), Swedish Cooperative (Ref. 15), and UK–TIA (Ref. 11). The agency evaluated the available data in the published reports, which in some cases differed from the data listing in the Trialists' reports (Refs. 16 and 20), because of their independent review of outcomes.

The SALT study (Ref. 22) compared aspirin (75 mg daily) and placebo in 1,360 subjects with a TIA, minor ischemic stroke, or retinal artery occlusion. Subjects were excluded if they had any of the following: (1) A potential cardiac source of emboli, including an MI, within 3 months prior to entry; (2) planned carotid surgery; (3) contraindications to aspirin; or (4) the need for long-term anticoagulation. The median duration of followup was 32 months. The primary outcome measure was all-cause mortality and stroke of any severity. The following were planned secondary analyses: (1) All strokes (fatal and nonfatal), (2) stroke or two or more TIA's within

1 week necessitating a change in therapy, and (3) all MI's (fatal and nonfatal). The primary and secondary outcome events are listed in Table 1 of this document.

TABLE 1.—PRIMARY AND SECONDARY OUTCOME EVENTS IN THE SALT STUDY

Primary events	Number of Subjects	
	Aspirin (n=676)	Placebo (n=684)
Primary events		
Nonfatal stroke		
Cerebral infarction, minor	55	68
Cerebral infarction, major	17	30
Intracerebral hemorrhage	4	3
Subarachnoid hemorrhage	1	1
Fatal stroke		
Cerebral infarction, major	10	7
Intracerebral hemorrhage	4	0
Subarachnoid hemorrhage	2	0
Unknown	0	3
Nonstroke deaths		
MI	18	28
Other vascular deaths	14	12
Malignant disorders	10	15
Other (infection, diabetes, trauma)	1	3
Unknown	2	1
Total primary outcome events	138	171
Secondary events		
Stroke (fatal and nonfatal)	93	112
Stroke or > 2 TIA's within 1 week, necessitating change in therapy	101	128
MI (fatal and nonfatal)	54	68

Log-rank analysis of stroke-free survival showed that aspirin was significantly superior to placebo ($p = 0.02$). Analysis of the same outcomes by "accumulated number of events" during the followup period showed a significant ($p = 0.05$) risk reduction of 18 percent (relative risk 0.82, 95 percent confidence interval 0.67 to 0.99) for nonfatal stroke or death. The risk reduction was similar in men and women (19 percent and 17 percent, respectively). More deaths were attributed to nonstroke events than to stroke in both the aspirin and placebo arms. Most of the nonstroke deaths in this study were attributed to MI, other vascular deaths, and malignant disorders. Fatal hemorrhagic stroke occurred in six subjects in the aspirin group and none in the placebo group ($p = 0.03$). Overall, more adverse effects were reported in the aspirin group than in the placebo group, particularly bleeding events (see Table 2 of this document).

TABLE 2.—ADVERSE EFFECTS OF ASPIRIN IN THE SALT STUDY

	Number (%) of Subjects	
	Aspirin	Placebo
Gastrointestinal (excluding bleeding)		
Total	85 (12.5)	73 (10.7)
Severe or causing discontinuation of study drug	21 (3.1)	18 (2.6)
Bleeding		

TABLE 2.—ADVERSE EFFECTS OF ASPIRIN IN THE SALT STUDY—Continued

	Number (%) of Subjects	
	Aspirin	Placebo
Total	49 (7.2)	22 (3.2)
Gastrointestinal	11 (1.6)	4 (0.6)
Intracranial	10 (1.5)	3 (0.4)
Other	28 (4.1)	15 (2.2)
Severe bleeding, or causing discontinuation of study drug	20 (3.0)	9 (1.3)
Gastrointestinal	9 (1.3)	4 (0.6)
Intracranial	10 (1.5)	3 (0.4)
Other	1 (0.1)	2 (0.3)
Other adverse effects		
Total	31 (4.6)	42 (6.1)
Severe, or causing discontinuation of study drug	9 (1.3)	11 (1.6)
Total number of subjects with adverse effects[1]	147 (21.7)	123 (18.0)

[1] Some subjects had more than one adverse effect.

The SALT study (Ref. 22) is generally a well-controlled and carefully done study that supports the use of low-dose aspirin to reduce the risk of death or stroke in subjects with TIA or minor ischemic stroke (see section II.A, comment 3 of this document).

The six additional studies identified were relatively small, except for the UK–TIA study. The Danish Cooperative study (Ref. 18) studied the effect of aspirin in subjects with reversible cerebral ischemic attack. The primary endpoint was stroke or death. TIA, reversible ischemic neurologic disability, and nonfatal MI were also monitored. The AICLA, Canadian Cooperative, AITIA, Swedish Cooperative, and UK–TIA studies are discussed in section II.A, comments 2 and 3 of this document. The Canadian Cooperative study and the AITIA study were also discussed in comment 49 of the TFM (53 FR 46204 at 46228 to 46230).

FDA performed a statistical analysis and tabulated the endpoints of all strokes and strokes plus death for these seven studies. The agency considered the overall combined results and estimated a common odds ratio for the selected set of available data. The SALT study was considered an independently positive study for the composite endpoint of stroke and death. To see whether that finding was substantiated by other data, the agency did a combined analysis for that endpoint that included all the studies except SALT. A summary of the entry criteria for the seven studies appears in Table 3 of this document.

TABLE 3.—STUDY CRITERIA OF CEREBROVASCULAR TRIALS

Study	Entry Criteria	n	Aspirin mg/day	Months followup
SALT	TIA, retinal artery occlusion, or minor stroke	1,360	75	32
AICLA	Cerebral or retinal ischemic event	402	990	36
Canadian	TIA or partial nonprogressing stroke	283	1,300	26
Fields	TIA	178	1,300	6 to 24
UK–TIA	TIA or minor ischemic stroke	2,435	1,200 or 300	48 (mean)
Danish	Reversible cerebral ischemic attack	203	1,000	43 (mean 24)
Swedish	Minor or major stroke due to cerebral infarction	505	1,500	24

The estimated odds ratios and 95 percent confidence intervals for aspirin versus placebo for the composite endpoint stroke and death (includes vascular and nonvascular) and for all strokes (includes fatal and nonfatal) are summarized in Table 4 of this document.

TABLE 4.—OUTCOME EVENTS OF CEREBROVASCULAR TRIALS

Study	Number of Events		Odds Ratio	95% Confidence Interval
	Aspirin	Placebo		
STROKES AND DEATHS				
AICLA	27/198	36/204	0.74	0.43, 1.26
Canadian	26/144	30/139	0.80	0.45, 1.44
Fields	13/88	19/90	0.65	0.30, 1.40
UK–TIA	382/1,621	220/814	0.83	0.68, 1.01
Danish	21/101	17/102	1.04	0.65, 2.65
Swedish	57/253	55/252	1.04	0.68, 1.58
All Studies	526/2,405	377/1,601	0.86	0.73, 0.999
ALL STROKES				
SALT	93/676	112/684	0.82	0.61, 1.10
AICLA	17/198	31/204	0.53	0.29, 0.98
Canadian	22/144	20/139	1.07	0.56, 2.06
Fields	11/88	14/90	0.78	0.33, 1.81
UK–TIA	163/1,621	98/814	0.81	0.62, 1.07
Danish	17/101	11/102	1.66	0.75, 3.68
Swedish	32/253	32/252	1.00	0.59, 1.68
All Studies	355/3,081	318/2,285	0.84	0.71, 0.99

Four of the seven studies showed trends in favor of aspirin for the endpoint of stroke, and five of seven for the composite endpoint of stroke and death, although most of them did not independently show a statistically significant difference between aspirin and placebo. Of the studies evaluated, only the AICLA study (Ref. 12) independently provides statistically significant results in favor of aspirin for the endpoint of stroke alone. The agency notes that the AICLA study was a small study that, when compared to the other studies, showed an unusually large magnitude of effect on stroke as an endpoint. A detailed report of the study was not submitted to the agency for review. Without a detailed report, the agency cannot draw definitive conclusions on the effect of aspirin on the endpoint of stroke alone based on this small study. However, the collective

evaluation of all the studies, including SALT, showed a statistically significant effect in favor of aspirin for the endpoint of stroke alone.

For the composite endpoint of stroke and death, the SALT study independently showed a statistically significant effect of aspirin compared to placebo in subjects with cerebrovascular problems. The collective results of the six other studies (without SALT) confirmed the finding (see Table 4 of this document). The composite endpoint of stroke and death in the studies evaluated includes those deaths attributed to cerebral, MI, and other fatal events.

On January 23, 1997, the Cardiovascular and Renal Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee (the Joint Advisory Committee) met to consider professional labeling for cardiovascular uses of aspirin. The Joint Advisory Committee unanimously recommended an indication for aspirin for subjects with prior occlusive stroke (both major and minor), pending the outcome of the agency's evaluation of the ESPS–2 (Ref. 23). The agency subsequently evaluated data from the aspirin (50 mg daily) and placebo arms of that study (Ref. 25). The study was a randomized, double blind, multicenter trial of about 6,600 subjects to show the effect of antiplatelet agents on subjects that had experienced TIA or completed ischemic stroke. After 2 years of treatment, the risk of stroke and the combined risk of stroke or death were reduced in the aspirin only arm compared to placebo.

Thus, the SALT study and the ESPS–2 study provide primary support for an indication for aspirin to reduce the combined risk of death or nonfatal stroke in subjects with TIA or ischemic stroke. The collective results of the six additional studies lend further support for this indication. Therefore, the agency is revising the indication as follows: "To reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli."

5. One comment recommended that the agency allow consumer-directed OTC labeling for the TIA, MI, unstable angina, and other thromboembolic indications, with complete information on warnings, recommended dosages, and side effects, provided the product is not advertised to

the general public. The comment also recommended that such labeling for these uses should be separate from any labeling for the analgesic, antipyretic, and antirheumatic uses of aspirin. The comment stated that aspirin is already widely used in the treatment of these non-analgesic conditions, and that it would be harmful to the public for the information not to be included in the consumer labeling.

Section 502(f) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(f)) states that a drug shall be deemed misbranded: ''Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions * * * where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users * * *.'' The directions for use or the warnings may be inadequate if the labeling refers to uses or conditions for which the drug can be safely used only under the supervision of a practitioner licensed by law (see 21 CFR 201.5). The agency considers the conditions and uses of aspirin that are the subject of this final rule to require the supervision of a physician (or other practitioner licensed to prescribe drugs) to ensure safe use. The agency therefore disagrees with the comment's recommendation.

Consumers are not in a position to determine when they need to take aspirin to prevent vascular events, such as stroke, MI, or cardiovascular death, and other thromboembolic conditions. The need for drug therapy and the safety of indicating it, for this purpose, is dependent on a variety of factors, including a person's medical history, age, gender, lifestyle, and concomitant medications. Medical intervention aimed at reducing the risk of any of these vascular events is both multifaceted and long term. In addition, intervention by a practitioner licensed to prescribe drugs is required for the ongoing management of the medical conditions being treated. Any prolonged use of aspirin has certain possible risks, e.g., increased or prolonged bleeding, GI hemorrhage, and ulceration. An increase in hemorrhagic stroke has also been reported (Refs. 4 and 5). It is not possible, in OTC drug product labeling, to provide adequate directions and warnings

to enable the layperson to make a reasonable self assessment of these factors. Therefore, safe and effective use of aspirin to influence the risk of vascular events requires medical supervision by a practitioner licensed to prescribe drugs.

An OTC drug, such as aspirin, may have some uses that can be properly labeled for direct consumer use and other uses that cannot be adequately labeled for direct consumer use. Professional labeling should be provided only to practitioners licensed to prescribe drugs, but not to the general public.

6. The agency also received a citizen petition (CP12) (Ref. 1) that requested an amendment to the professional labeling for aspirin in secondary prevention of cardiovascular morbidity and mortality in men and women at elevated risk for cardiovascular events. The petition's requests for professional labeling for aspirin included indications for: (1) Patients undergoing coronary, cerebral, or peripheral arterial revascularization procedures; (2) patients with chronic nonvalvular atrial fibrillation; (3) patients requiring hemodialysis access with a fistula or shunt; and (4) other patients deemed to be at elevated risk due to some form of vascular disease or other condition implying an increased risk of occlusive vascular disease. The authors of the petition subsequently clarified that they were requesting an aspirin indication, at a maintenance dose of at least 75 to 81 mg per day, only for those patients who have already been diagnosed as having had some occlusive arterial disease and who currently have no special contraindications to low-dose aspirin. The petition also included information on the use of aspirin for subjects with chronic stable angina pectoris. The agency evaluated the petition and presented its review of the petition at a meeting on April 25, 1996. Minutes of that meeting, including the agency's review of the petition, are on file in the Dockets Management Branch (Ref. 26). The petition cited published reports of two studies as support for an indication for chronic stable angina pectoris. The first study was the Swedish Angina Pectoris Aspirin Trial (SAPAT) (Ref. 27), and the second study was an assessment of those male physicians who entered the U.S. Physicians' Health Study with chronic stable angina (Ref. 28).

The SAPAT study was a randomized, multicenter, double-blind, prospective study designed to assess the role of aspirin for prevention of MI in 2,035 subjects with chronic stable angina pectoris. Subjects were randomized to receive daily doses of either 75 mg of aspirin plus sotalol (aspirin group) or placebo plus sotalol (placebo group) daily. The primary endpoint of the study was the combined rates of first fatal or nonfatal MI or sudden death. Secondary endpoints were vascular events (first occurrence of nonfatal MI, nonfatal stroke, or vascular death), vascular death, all-cause mortality, and stroke. Primary and secondary endpoint data appear in Table 5 of this document.

TABLE 5.—PRIMARY AND SECONDARY ENDPOINTS IN THE SAPAT STUDY

Endpoint	Aspirin + Sotalol n=1,009	Placebo + Sotalol n=1,026	Percent Change	p
Primary:	81	124	-34	.003
nonfatal MI	47	78	-3.9	.006
fatal MI	15	15	0	
sudden death	19	31	-38	.097
Secondary:				
vascular events	108	161	-32	<.001
vascular deaths	51	70	-26	.114
all cause mortality	82	106	-22	.103
stroke	28	38	-25	.246
hemorrhagic	5	2		
nonhemorrhagic	23	36		

The SAPAT study supports the use of 75 mg aspirin daily in subjects with chronic stable angina pectoris. The study showed a significant reduction in the primary endpoint of fatal or nonfatal MI and sudden death, and the secondary endpoint of vascular events (first occurrence of MI, stroke, or vascular death). The study also showed a significant overall reduction in a major component of the primary endpoint, nonfatal MI. Although the decreases in vascular deaths and all cause mortality were not statistically significant, there was a favorable trend in the aspirin group for both of these endpoints and a weakly favorable trend for stroke. There were more reports of serious bleeds in the aspirin group than in the placebo group, but the difference was not significant. As in many other studies, however, there were more hemorrhagic strokes in the aspirin group than the placebo group. All the subjects in the SAPAT study were treated with sotalol. Therefore, the question arises as to whether it can be concluded that aspirin is effective in angina patients not receiving sotalol (or some other beta blocker). Although there are not specific data

on this point, the ability of aspirin to decrease the rate of thrombotic vascular events in various settings has not required or, to date, been related to, the presence or absence of beta blockers. Therefore, the agency concludes that the SAPAT study supports the use of aspirin in patients with chronic stable angina, with or without sotalol.

The agency presented a summary of its findings for the SAPAT study at the meeting of the Joint Advisory Committee on January 23, 1997. The Joint Advisory Committee unanimously agreed that the SAPAT study supports the use of aspirin in subjects with chronic stable angina pectoris, and that an indication for low-dose aspirin should be extended to that population.

Ridker et al. (Ref. 28) assessed those subjects with chronic stable angina who entered the U.S. Physicians' Health Study (Ref. 4). The authors concluded that aspirin therapy reduced the risk of first MI among patients with chronic stable angina. However, the agency found that some of the subjects entered into the U.S. Physicians' Health Study had evidence of a previous MI. Thus, it is possible that in the subgroup of subjects with chronic stable angina pectoris, some subjects may also have had a previous MI. Aspirin has already been shown to be effective in subjects with a previous MI and, therefore, some of the positive results found in the Ridker study may in part be due to aspirin's demonstrated effectiveness in patients with previous MI. Nevertheless, the results of the Ridker study are consistent with the findings in the SAPAT study, and lend some additional support for an indication for aspirin for subjects with chronic stable angina pectoris.

The agency is, therefore, extending the indication for aspirin for cardiovascular uses in proposed § 343.80(c) to include reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris. This conclusion is also supported by substantial additional controlled trials in other populations with coronary artery disease that show reduced risk for similar endpoints, specifically patients with a prior MI. The dosage range is also revised from "300 to 325 mg daily" to "75 to 325 mg daily," to include the lower dose used in the SAPAT study, and the "Clinical Studies" section of the professional labeling includes information on this study.

The agency has considered the petition's request for an indication for aspirin for subjects who have undergone revascularization procedures including coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), carotid endarterectomy, peripheral artery grafts, peripheral arterial fistula or shunt, or peripheral angioplasty. The agency considered the published reports submitted by the petitioner that evaluated aspirin alone in one arm versus a placebo or other active ingredient, and additional information from the report of the Fourth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy (Ref. 29). The agency concluded (Ref. 26) that there was insufficient evidence, based on the published studies, to support the professional labeling of aspirin alone in patients who have undergone revascularization procedures, although some studies have suggested benefit in these patients (Refs. 30 through 34).

The issue of aspirin use in patients who have undergone revascularization procedures was considered by the Joint Advisory Committee on January 23, 1997. The panel members concluded that specific studies have not been presented to show effectiveness of aspirin for this population. However, they noted that almost all patients who undergo coronary revascularization procedures have already had symptomatic coronary disease, such as stable or unstable angina or MI. The Joint Advisory Committee recommended unanimously that aspirin be recommended for subjects who have undergone revascularization procedures such as CABG or PTCA if there is a preexisting condition for which aspirin is already indicated. However, the Joint Advisory Committee made no specific recommendation regarding the use of aspirin in subjects who have undergone carotid endarterectomy.

The agency agrees with the Joint Advisory Committee's recommendation that the professional labeling of aspirin should include subjects who have undergone revascularization procedures for symptomatic coronary artery disease. It is a reasonable assumption that, in general, subjects who have had CABG or PTCA procedures have an underlying condition for which aspirin is indicated. Similarly, the agency believes subjects with lesions of the carotid bifurcation sufficient to require

carotid endarterectomy are likely to have had a TIA or stroke, and may also have coexisting coronary artery disease (Ref. 34). Therefore, the agency is adding an indication to the professional labeling for subjects who have had specific arterial revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy). Likewise, the agency believes it is reasonable to recommend the standard dosages being used in clinical practice (Refs. 35 through 37) during the preoperative period. The following dosages are included in this final rule: CABG, 325 mg daily, starting 6 hours post-procedure and continued 1 year; PTCA, 325 mg 2 hours presurgery, followed by maintenance therapy of 160 to 325 mg daily; and carotid endarterectomy, 80 mg daily to 650 mg twice daily preoperatively and continued indefinitely.

The issue of an indication for aspirin for subjects with peripheral arterial disease was also considered by the Joint Advisory Committee. The Joint Advisory Committee concluded that the trials that used aspirin alone showed no effect on subjects with peripheral arterial disease, despite a sizable data base in which to examine this effect. By a vote of 11 to 4, the members recommended not to label aspirin for the indication. The agency agrees with the Committee and concludes that there is insufficient data to support professional labeling for aspirin alone in subjects with peripheral arterial disease, including subjects with and without peripheral artery grafts or peripheral angioplasty.

The petitioner has withdrawn the request for an indication for aspirin for subjects requiring hemodialysis access with a fistula or shunt, and for subjects with atrial fibrillation (Ref. 38).

B. Comments to the Proposal to Include Acute MI in Professional Labeling of Aspirin

7. The agency received four comments (Ref. 2) that addressed the need for additional warnings relating to the use of aspirin for cardiovascular and cerebrovascular indications. Two comments recommended that additional information about adverse events be included in the professional and consumer labeling. Two comments argued against the need for additional warnings.

One comment recommended that professional aspirin labeling be revised to provide the following: (1) Information for physicians on the risk of adverse GI effects associated with the

long-term use of low-dose aspirin, and (2) advice to physicians concerning appropriate analgesic and antipyretic use in their patients who are taking long-term low-dose aspirin for cardiovascular indications. The comment further recommended that consumer aspirin labeling should be revised to: (1) Alert consumers to the signs and symptoms of adverse events that might occur with therapeutic (labeled) doses of aspirin, and (2) advise patients that they should consult their physician prior to any analgesic use for pain or fever relief if they are taking low-dose aspirin under a physician's care for cardiovascular indications. The comment asserted that adverse GI effects are present with aspirin in doses as low as 30 mg per day and that the risk of adverse GI events increases as the aspirin dose increases. In support of this position, the comment included literature articles (Refs. 4, 11, 22, and 39 through 46).

Another comment acknowledged that adverse events from aspirin use have been carefully studied and characterized, and stated that even at the highest doses studied, 1,500 mg per day, the incidence of serious adverse events is small. The comment noted that the internal analgesic TFM proposes a total daily aspirin dose of 4,000 mg for acute pain management. The comment concluded that none of the studies cited by the first comment demonstrate that a person taking 75 to 325 mg per day of aspirin is at risk of adverse events other than those already labeled if additional aspirin is taken for short-term analgesic or antipyretic use. The comment concluded that labeling should not be proposed which could interfere with a physician's guidance to a patient, and that aspirin should not be singled out for special consideration. One comment noted that professional labeling already includes information concerning adverse reactions and no further changes are necessary.

The agency agrees that physicians should be provided information on potential adverse events from long-term low-dose aspirin use. The agency believes this information should not be limited to potential adverse GI events, but that professional labeling should include complete prescribing information for practitioners licensed to prescribe drugs. Therefore, the agency has developed aspirin professional labeling containing the type of prescribing information included in prescription

drug labeling in a format similar to that required for prescription drugs under §§ 201.56 and 201.57. In addition, the agency has consolidated all of the professional uses of aspirin into a single labeling format. The final aspirin professional labeling also includes an optional highlights section that summarizes the professional indications for aspirin and the recommended dosage and administration for each indication. The highlights section, if disseminated, must accompany the required professional labeling as provided in § 343.80(a). Dissemination of the highlights section, however, is not required.

This professional labeling also includes complete information on adverse reactions. The labeling states, "Many adverse reactions due to aspirin ingestion are dose-related." Among the adverse reactions listed are GI bleeding, ulceration, and perforation, as requested by the comment. Also, this labeling warns against concurrent use of aspirin with other analgesics with similar adverse drug event profiles because this may result in an increase in adverse drug reactions, and it includes a warning regarding bleeding risks associated with chronic, heavy use of alcohol. (See the final rule published elsewhere in this issue of the **Federal Register** entitled "Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use; Required Alcohol Warning".)

The agency does not believe that this labeling will interfere with a physician's guidance to a patient. Rather, both the content and the format of the labeling is expected to enhance appropriate choices.

The agency will address consumer aspirin labeling in the final rule for internal analgesic, antipyretic, and antirheumatic drug products, which will be published in a future issue of the **Federal Register**.

8. One comment asked the agency to include an indication for acute MI in OTC consumer drug labeling. The comment stated that a significant number of people who die of heart attacks do so beyond the reach of health-care providers. The comment argued that by limiting the proposed indication to professional labeling, the agency neglects consumers at risk for heart attack. The

comment said that this population needs to know that a half an aspirin can reduce their risk of cardiovascular morbidity and mortality. The comment also recommended a warning stating that patients should seek immediate diagnosis and treatment by a doctor.

The issue of whether consumer labeling is appropriate for an indication such as acute MI is addressed generally in section II.A, comment 5 of this document. The agency will address consumer aspirin labeling in the final rule for internal analgesic, antipyretic, and antirheumatic drug products, which will be published in a future issue of the **Federal Register**.

9. One comment asked the agency to consider several proposed wording changes. The comment suggested changing the proposed sentence "a dose of 162.5 mg/day, started as soon as possible after a suspected infarction" to "a dose of 162.5 mg/day, started as soon as possible during' a suspected infarction." The comment suggested that the current wording is misleading and implies that treatment not be initiated until a diagnosis of infarction is established.

The agency agrees that the dosing information for suspected acute MI should be revised to emphasize the immediate use of aspirin for suspected acute MI. However, the agency believes that instructions for the initial dose of aspirin to be administered "as soon as an MI is suspected" better conveys the need for immediate action and has included this information in the professional labeling for suspected acute MI.

10. One comment recommended a dosage range of 162.5 to 325 mg aspirin per day for suspected acute MI. In support of its request, the comment cited the results of the ISIS–2 and ISIS pilot studies. The comment suggested that this dosage range for suspected acute MI is more consistent with agency dosing recommendations for other professional labeling indications for aspirin, e.g., 300 to 325 mg aspirin for the prevention of a second heart attack.

In the preamble to the proposed rule for the use of aspirin, buffered aspirin, and aspirin/ antacid combinations to reduce the risk of vascular mortality in people with suspected acute MI (61 FR 30002), the agency discussed the basis for its conclusions on the effective dose of aspirin for this use. The results of the ISIS–2 study (162.5 mg aspirin per day) (Ref. 7) were accepted

by the agency as the primary support for the indication. Concerning the ISIS pilot study (Ref. 47), the agency noted that a 325 mg aspirin dose every other day produced: (1) A nonsignificant reduction in nonfatal reinfarction, (2) a significantly lower rate of in-hospital deaths (all causes), and (3) similar rates of post-hospital deaths (61 FR 30005). Therefore, the ISIS pilot study does not provide a basis to support a 325 mg aspirin dose for suspected acute MI and this dose is not included in this final rule.

III. Summary of Changes

1. The TFM for OTC analgesic, antipyretic, and antirheumatic drug products included an indication for the professional use of aspirin, carbaspirin calcium, magnesium salicylate, or sodium salicylate for rheumatologic diseases (53 FR 46204 at 46244). The indication was based on the recommendations of the Panel made in 1977. No comments were received in response to the TFM concerning this indication. The indication for the use of aspirin in rheumatologic diseases has been updated. For completeness, the agency has included full prescribing information for the professional uses of aspirin, including full information for the treatment of the signs and symptoms of rheumatologic disease. However, professional labeling on the use of other Category I salicylates for rheumatologic diseases has not been included and will be addressed in the final rule for OTC internal analgesic, antipyretic, and antirheumatic drug products to be published in a future issue of the **Federal Register**.

2. To allow for the codification of the professional labeling, the agency is: (1) Finalizing certain sections of the proposed rule pertaining to scope, definitions, and testing procedures that apply to both OTC and professional labeling; (2) adding definitions in § 343.3; and (3) adding §§ 343.12, 343.13 and 343.22 which include cardiovascular and rheumatologic active ingredients and permitted combinations of active ingredients.

3. The heading for § 343.90 under "Testing Procedures" has been changed from "Dissolution testing" to "Dissolution and drug release testing" to include the current United States Pharmacopeia (USP) terminology for testing delayed-release products. The agency has updated the

dissolution tests in § 343.90 from those contained in USP XXI, which were in effect when the TFM was published, to those currently in effect in USP 23. The dissolution testing procedures have been added for aspirin, alumina, and magnesium oxide tablets and aspirin effervescent tablets for oral solution in § 343.90(f) and (g), respectively. (A monograph for these products were included in the USP after publication of the TFM.) Proposed § 343.90(f) for buffered aspirin tablets is now § 343.90(h).

4. The minimum dosages for the vascular indications in this final rule are lower than those proposed in the TFM. The agency is concerned about the impact of formulation on the effectiveness of the lower-dose aspirin. Therefore, this final rule allows professional labeling only for those products that meet USP dissolution and drug release standards in § 343.90.

5. In the TFM, the agency proposed professional labeling indications for TIA and rheumatologic diseases for aspirin and buffered aspirin drug products identified in § 343.10(b), except those buffered with sodium. The TFM did not include these indications for aspirin in combination with antacids identified in § 343.20(b)(3). The agency is expanding the professional labeling indications for TIA and rheumatologic diseases in this final rule to include aspirin drug products buffered with sodium and aspirin in combination with antacid. The agency has taken this action based on: (1) The additional prescribing information included in this final rule on the use of sodium-containing products in patients who need to restrict their sodium intake; (2) data that show there is no significant difference between the plasma aspirin levels obtained with aspirin, buffered aspirin, and aspirin in combination with antacids (Refs. 48 and 49); (3) the lower dosage of aspirin for TIA; and (4) the physician's routine practice of titrating the dosage of aspirin to an effective blood level for rheumatologic diseases.

6. Portions of the proposed rule would have amended 21 CFR 310.201, 369.20, and 369.21. This final rule is one segment of the proposed rule and does not affect these sections. The other portions of the proposed rule will be discussed in a future issue of the **Federal Register**.

IV. References

The following references are on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Comment Nos. C146, C153, C154, C155, CP9, CP10, and CP12, Docket No. 77N–0094, Dockets Management Branch.

(2) Comment Nos. C1–C10, Docket No. 77N–0094A, Dockets Management Branch.

(3) Steering Committee of the Physicians' Health Study Research Group, "Preliminary Report: Findings from the Aspirin Component of the Ongoing Physicians' Health Study," *New England Journal of Medicine*, 318:262–264, 1988.

(4) Steering Committee of the Physicians' Health Study Research Group, "Final Report on the Aspirin Component of the Ongoing Physicians' Health Study," *New England Journal of Medicine*, 321:129–135, 1989.

(5) Peto, R. et al., "Randomized Trial of Prophylactic Daily Aspirin in British Male Doctors," *British Medical Journal*, 296:313–316, 1988.

(6) Manson, J. E. et al., "Medical Progress: The Primary Prevention of Myocardial Infarction," *New England Journal of Medicine*, 326:1406–1416, 1992.

(7) ISIS–2 (Second International Study Of Infarct Survival) Collaborative Group, "Randomized Trial of Intravenous Streptokinase, Oral Aspirin, Both, or Neither Among 17,187 Cases of Suspected Acute Myocardial Infarction: ISIS–2," *Lancet*, 2:349–360, 1988.

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(9) Yusef, S., "Analysis and Interpretation of Treatment Effects in Subgroups of Patients in Randomized Clinical Trials," *Journal of the American Medical Association*, 266:93–98, 1991.

(10) Fields, W. S. et al., "Controlled Trial of Aspirin in Cerebral Ischemia," *Stroke*, 8:301–316, 1977.

(11) UK–TIA Study Group, "United Kingdom Transient Ischaemic Attack (UK–TIA) Aspirin Trial: Interim Results," *British Medical Journal*, 296:316–320, 1988.

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(14) The American-Canadian Co-Operative Study Group, "Persantine Aspirin Trial in Cerebral Ischemia Part II: Endpoint Results," *Stroke*, 16:406–415, 1985.

(15) A Swedish Cooperative Study, "High-Dose Acetylsalicylic Acid after Cerebral Infarction," *Stroke*, 18:325–334, 1987.

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(17) Fields, W. S. et al., "Controlled Trial of Aspirin in Cerebral Ischemia. Part II: Surgical Group," *Stroke*, 9:309–318, 1978.

(18) Sorensen, P. S. et al., "Acetylsalicylic Acid in the Prevention of Stroke in Patients with Reversible Cerebral Ischemic Attacks. A Danish Cooperative Study," *Stroke*, 14:15–22, 1983.

(19) Reuther, R., and W. Dorndorf, "Aspirin in Patients with Cerebral Ischemia and Normal Angiograms. The Results of a Double Blind Trial," in *Acetylsalicylic Acid in Cerebral Ischaemic and Coronary Artery Disease*, edited by Breddin, K. et al., Schatauer Verlag, Stuttgart Germany, pp. 97–106, 1978.

(20) Antiplatelet Trialists' Collaboration, "Collaborative Overview of Randomized Trials of Antiplatelet Therapy—I: Prevention of Death, Myocardial Infarction, and Stroke by Prolonged Antiplatelet Therapy in Various Categories of Patients," *British Medical Journal*, 308:81–106, 1994.

(21) Boysen, G. et al., "Danish Very-Low-Dose Aspirin after Carotid Endarterectomy Trial," *Stroke*, 19:1211–1215, 1988.

(22) The SALT Collaborative Group, "Swedish Aspirin Low-Dose Trial (SALT) of 75 mg Aspirin as Secondary Prophylaxis after Cerebrovascular Ischaemic Events," *Lancet*, 338:1345–1349, 1991.

(23) Diener, H. C. et al., "European Stroke Prevention Study 2. Dipyridamole and Acetylsalicylic Acid in the Secondary Prevention of Stroke," *Journal of Neurological Sciences*, 143:1–13, 1996.

(24) Matchar, D. B. et al., "Medical Treatment for Stroke Prevention," *Annals of Internal Medicine*, 121:41–53, 1994.

(25) FDA evaluation of ESPS–2 data, OTC Volume 03BFMP, Docket No. 77N–0094, Dockets Management Branch.

(26) Minutes of Meeting between representatives of FDA and The Aspirin Strategy Group, on April 25, 1996, Coded MM21, Docket No. 77N–0094, Dockets Management Branch.

(27) Juul-Möller, S. et al., "Double-Blind Trial of Aspirin in Primary Prevention of Myocardial Infarction in Patients with Stable Chronic Angina Pectoris," *Lancet*, 340:1421–1425, 1992.

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(29) Dalen, J. E., and J. Hirsh, (Guest Editors), Fourth ACCP Consensus Conference on Antithrombotic Therapy, *Chest*, 108:225S–522S, October 1995 (Supplement).

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V. Analysis of Impacts

An analysis of the costs and benefits of this regulation conducted under Executive Order 12291 was discussed in the TFM for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46204 at 46254). No comments on the economic impact related to professional labeling for aspirin were received in response to the agency's request for specific comment on the economic impact of this rulemaking. Executive Order 12291 has been superseded by Executive Order 12866.

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and, thus, is not subject to review under the Executive Order. This rule also does not trigger the requirement for a written statement under section 202(a) of the Unfunded Mandates Reform Act

because it does not impose a mandate that results in an expenditure of $100 million or more by State, local, and tribal governments in the aggregate, or by the private sector, in any 1 year.

If a rule would have a significant impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize the impact of the rule on small entities. This final rule will impose direct one-time costs associated with changing professional labeling to reflect current information. In the June 13, 1996 (61 FR 30002 at 30007), amendment to the TFM, the agency certified that the rule would not have a significant economic impact on a substantial number of small entities, based on the fact that few manufacturers of aspirin products appear to distribute professional labeling for their products and that manufacturers who do distribute such professional labeling will have 1 year after publication of this final rule to implement this relabeling. The economic impact of this final rule on manufacturers appears to be minimal. The agency did not receive any comments challenging the basis for its initial proposed certification. Accordingly, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

VI. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this final rule are not subject to review by the Office of Management and Budget because they do not constitute a ''collection of information'' under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling statements are a ''public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public'' (5 CFR 1320.3(c)(2)).

VII. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 343

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR Chapter I is amended as follows:

1. Part 343 is added to read as follows:

PART 343—INTERNAL ANALGESIC, ANTIPYRETIC, AND ANTIRHEUMATIC DRUG PRODUCTS FOR OVER–THE–COUNTER HUMAN USE

Subpart A—General Provisions

Sec.

Subpart B—Active Ingredients

Subpart C—Labeling

Subpart D—Testing Procedures

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

Subpart A—General Provisions

§ 343.1 Scope.

(a) An over-the-counter analgesic-antipyretic drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this part in addition to each of the general conditions established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21 unless otherwise noted.

§ 343.3 Definitions.

As used in this part:

Analgesic-antipyretic drug. An agent used to alleviate pain and to reduce fever.

Cardiovascular drug. An agent used to prevent ischemic events.

Rheumatologic drug. An agent used for the treatment of rheumatologic disorders.

Subpart B—Active Ingredients

§ 343.10 [Reserved]

§ 343.12 Cardiovascular active ingredients.

(a) Aspirin.

(b) Buffered aspirin. Aspirin identified in paragraph (a) of this section may be buffered with any antacid ingredient(s) identified in § 331.11 of this chapter provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing capacity per 325 milligrams of aspirin as measured by the procedure provided in the United States Pharmacopeia 23/National Formulary 18.

§ 343.13 Rheumatologic active ingredients.

(a) Aspirin.

(b) Buffered aspirin. Aspirin identified in paragraph (a) of this section may be buffered with any antacid ingredient(s) identified in § 331.11 of this chapter provided that the finished product contains at least 1.9 milliequivalents of acid-neutralizing capacity per 325 milligrams of aspirin as measured by the procedure provided in the United States Pharmacopeia 23/National Formulary 18.

§ 343.20 [Reserved]

§ 343.22 Permitted combinations of active ingredients for cardiovascular-rheumatologic use.

Combinations containing aspirin must meet the standards of an acceptable dissolution test, as set forth in § 343.90. The following combinations are permitted: Aspirin identified in §§ 343.12 and 343.13 may be combined with any antacid ingredient identified in § 331.11 of this chapter or any combination of antacids permitted in accordance with § 331.10(a) of this chapter provided that the finished product meets the requirements of § 331.10 of this chapter and is marketed in a form intended for ingestion as a solution.

Subpart C—Labeling

§ 343.50 [Reserved]

§ 343.60 [Reserved]

§ 343.80 Professional labeling.

The labeling of an over-the-counter drug product written for health professionals (but not for the general public) shall consist of the following:

(a) *For products containing aspirin identified in §§ 343.12 and 343.13 or permitted combinations identified in § 343.22.* (These products must meet United States Pharmacopeia (USP) standards for dissolution or drug release in § 343.90.)

(1) The labeling contains the following prescribing information under the heading ''Comprehensive Prescribing Information'' and the subheadings ''Description,'' ''Clinical Pharmacology,'' ''Clinical Studies,'' ''Animal Toxicology,'' ''Indications and Usage,'' ''Contraindications,'' ''Warnings,'' ''Precautions,'' ''Adverse Reactions,'' ''Drug Abuse and Dependence,'' ''Overdosage,'' ''Dosage and Administration,'' and ''How Supplied'' in the exact language and the exact order provided below.

COMPREHENSIVE PRESCRIBING INFORMATION

DESCRIPTION

(*Insert the proprietary name and the established name (if any) of the drug, type of dosage form (followed by the phrase ''for oral administration''), the established name(s) and quantity of the active ingredient(s) per dosage unit, the total sodium content in milligrams per dosage unit if the sodium content of a single recommended dose is 5 milligrams or more, the established name(s) (in alphabetical order) of any inactive ingredient(s) which may cause an allergic hypersensitivity reaction, the pharmacological or therapeutic class of the drug, and the chemical name(s) and structural formula(s) of the drug.*) Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary-odor. It is highly lipid soluble and slightly soluble in water.

CLINICAL PHARMACOLOGY

Mechanism of Action: Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclo-oxygenase via acetylation.

PHARMACOKINETICS

Absorption: In general, immediate release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1–2 hours of dosing (see **Pharmacokinetics**—*Metabolism*). The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents), and other physiologic factors. Enteric coated aspirin products are erratically absorbed from the GI tract.

Distribution: Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is concentration-dependent, i.e., non-linear. At low concentrations (< 100 micrograms/milliliter (µg/mL)), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (> 400 µg/mL), only about 75 percent is bound. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 µg/mL. Severe toxic effects are associated with levels > 400 µg/mL. (See **Adverse Reactions** and **Overdosage**.)

Metabolism: Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1–2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10–20 grams (g)), the plasma half-life may be increased to over 20 hours.

Elimination: The elimination of salicylic acid follows zero order pharmacokinetics; (i.e., the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5 percent to > 80 percent. Alkalinization of the urine is a key concept in the management of

salicylate overdose. (See **Overdosage**.) Following therapeutic doses, approximately 10 percent is found excreted in the urine as salicylic acid, 75 percent as salicyluric acid, as the phenolic and acyl glucuronides, respectively.

Pharmacodynamics: Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A2. Non-acetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I_2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

At higher doses aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-oxygenase inhibition in peripheral tissues. In vitro studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated. It is this non-specific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation. (See **Adverse Reactions**.)

CLINICAL STUDIES

Ischemic Stroke and Transient Ischemic Attack (TIA): In clinical trials of subjects with TIA's due to fibrin platelet emboli or ischemic stroke, aspirin has been shown to significantly reduce the risk of the combined endpoint of stroke or death and the combined endpoint of TIA, stroke, or death by about 13–18 percent.

Suspected Acute Myocardial Infarction (MI): In a large, multi-center study of aspirin, streptokinase, and the combination of aspirin and streptokinase in 17,187 patients with suspected acute MI, aspirin treatment produced a 23-percent reduction in the risk of vascular mortality. Aspirin was also shown to have an additional benefit in patients given a thrombolytic agent.

Prevention of Recurrent MI and Unstable Angina Pectoris: These indications are supported by the results of six large, randomized, multi-center, placebo-controlled trials of predominantly male post-MI subjects and one randomized placebo-controlled study of men with unstable angina pectoris. Aspirin therapy

in MI subjects was associated with a significant reduction (about 20 percent) in the risk of the combined endpoint of subsequent death and/or nonfatal reinfarction in these patients. In aspirin-treated unstable angina patients the event rate was reduced to 5 percent from the 10 percent rate in the placebo group.

Chronic Stable Angina Pectoris: In a randomized, multi-center, double-blind trial designed to assess the role of aspirin for prevention of MI in patients with chronic stable angina pectoris, aspirin significantly reduced the primary combined endpoint of nonfatal MI, fatal MI, and sudden death by 34 percent. The secondary endpoint for vascular events (first occurrence of MI, stroke, or vascular death) was also significantly reduced (32 percent).

Revascularization Procedures: Most patients who undergo coronary artery revascularization procedures have already had symptomatic coronary artery disease for which aspirin is indicated. Similarly, patients with lesions of the carotid bifurcation sufficient to require carotid endarterectomy are likely to have had a precedent event. Aspirin is recommended for patients who undergo revascularization procedures if there is a preexisting condition for which aspirin is already indicated.

Rheumatologic Diseases: In clinical studies in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis and osteoarthritis, aspirin has been shown to be effective in controlling various indices of clinical disease activity.

ANIMAL TOXICOLOGY

The acute oral 50 percent lethal dose in rats is about 1.5 g/kilogram (kg) and in mice 1.1 g/kg. Renal papillary necrosis and decreased urinary concentrating ability occur in rodents chronically administered high doses. Dose-dependent gastric mucosal injury occurs in rats and humans. Mammals may develop aspirin toxicosis associated with GI symptoms, circulatory effects, and central nervous system depression. (See **Overdosage.**)

INDICATIONS AND USAGE

Vascular Indications (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, and Chronic Stable Angina Pectoris): Aspirin is indicated to: (1) Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain

due to fibrin platelet emboli, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures (Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), and Carotid Endarterectomy): Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

Rheumatologic Disease Indications (Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Spondyloarthropathies, Osteoarthritis, and the Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE)): Aspirin is indicated for the relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with SLE.

CONTRAINDICATIONS

Allergy: Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

Reye's Syndrome: Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

WARNINGS

Alcohol Warning: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities: Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GI Side Effects: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Peptic Ulcer Disease: Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

PRECAUTIONS

General

Renal Failure: Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

Hepatic Insufficiency: Avoid aspirin in patients with severe hepatic insufficiency.

Sodium Restricted Diets: Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.

Laboratory Tests: Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Drug Interactions

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin

from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-inflammatory Drugs (NSAID's): The concurrent use of aspirin with other NSAID's should be avoided because this may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Administration of aspirin for 68 weeks at 0.5 percent in the feed of rats was not carcinogenic. In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Aspirin inhibits ovulation in rats. (See *Pregnancy.*)

Pregnancy: Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAID's on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

Labor and Delivery: Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Nursing Mothers: Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

Pediatric Use: Pediatric dosing recommendations for juvenile rheumatoid arthritis are based on well-controlled clinical studies. An initial dose of 90–130 mg/kg/day in divided doses, with an increase as needed for anti-inflammatory efficacy (target plasma salicylate levels of 150–300 μg/mL) are effective. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.

ADVERSE REACTIONS

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature. (See **Warnings**.)

Body as a Whole: Fever, hypothermia, thirst.

Cardiovascular: Dysrhythmias, hypotension, tachycardia.

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.

Fluid and Electrolyte: Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's Syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.

Hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

Musculoskeletal: Rhabdomyolysis.

Metabolism: Hypoglycemia (in children), hyperglycemia.

Reproductive: Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

Respiratory: Hyperpnea, pulmonary edema, tachypnea.

Special Senses: Hearing loss, tinnitus. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

DRUG ABUSE AND DEPENDENCE

Aspirin is non-narcotic. There is no known potential for addiction associated with the use of aspirin.

OVERDOSAGE

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approaching 200 µg/mL. Plasma concentrations of aspirin above 300 µg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 µg/mL. (See **Clinical Pharmacology**.) A single lethal dose of aspirin in adults is not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.

Signs and Symptoms: In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.

Treatment: Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying and/or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage and/or emesis, administration of activated charcoal, as a slurry, is beneficial, if less than 3 hours have passed since ingestion. Charcoal adsorption should not be employed prior to emesis and lavage.

Severity of aspirin intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gas and serum pH measurements. Fluid and electrolyte balance should also be maintained.

In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

DOSAGE AND ADMINISTRATION

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted. Anti-inflammatory and analgesic dosages should be individualized. When aspirin is used in high doses, the development of tinnitus may be used as a clinical sign of elevated plasma salicylate levels except in patients with high frequency hearing loss.

Ischemic Stroke and TIA: 50–325 mg once a day. Continue therapy indefinitely.

Suspected Acute MI: The initial dose of 160–162.5 mg is administered as soon as an MI is suspected. The maintenance dose of 160–162.5 mg a day is continued for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.

Prevention of Recurrent MI: 75–325 mg once a day. Continue therapy indefinitely.

Unstable Angina Pectoris: 75–325 mg once a day. Continue therapy indefinitely.

Chronic Stable Angina Pectoris: 75–325 mg once a day. Continue therapy indefinitely.

CABG: 325 mg daily starting 6 hours post-procedure. Continue therapy for 1 year post-procedure.

PTCA: The initial dose of 325 mg should be given 2 hours pre-surgery. Maintenance dose is 160–325 mg daily. Continue therapy indefinitely.

Carotid Endarterectomy: Doses of 80 mg once daily to 650 mg twice daily, started presurgery, are recommended. Continue therapy indefinitely.

Rheumatoid Arthritis: The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 μg/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.

Juvenile Rheumatoid Arthritis: Initial dose is 90–130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 μg/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.

Spondyloarthropathies: Up to 4 g per day in divided doses.

Osteoarthritis: Up to 3 g per day in divided doses.

Arthritis and Pleurisy of SLE: The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150–300 μg/mL. At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.

HOW SUPPLIED

(*Insert specific information regarding, strength of dosage form, units in which the dosage form is generally available, and information to facilitate identification of the dosage form as required under § 201.57(k)(1), (k)(2), and (k)(3).) Store in a tight container at 25* °C (77 °F); excursions permitted to 15–30 °C (59–86 °F).

REV: (*insert date of publication in the* **Federal Register**.)

(2) In addition to, and immediately preceding, the labeling required under paragraph (a)(1) of this section, the professional labeling may contain the following highlights of prescribing information in the exact language and exact format provided below, but only when accompanied by the comprehensive prescribing information required in paragraph (a)(1) of this section.

[Insert graphic]

HIGHLIGHTS OF PRESCRIBING INFORMATION
ASPIRIN (FORMULATION)
(acetylsalicylic acid)

PROFESSIONAL INDICATIONS AND USAGE
Vascular Indications:
· Ischemic Strokes and Transient Ischemic Attacks (TIA)
· Suspected Acute Myocardial Infarction (MI)
· Prevention of Recurrent MI
· Unstable Angina Pectoris
· Chronic Stable Angina Pectoris
Revascularization Procedures in Select Patients:[1]
· Coronary Artery Bypass Graft (CABG)
· Percutaneous Transluminal Coronary Angioplasty (PTCA)
· Carotid Endarterectomy
Rheumatologic Disease Indications:
· Rheumatoid Arthritis
· Juvenile Rheumatoid Arthritis
· Spondyloarthropathies
· Osteoarthritis
· Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE)

Warnings Regarding Use in Pregnancy
Pregnant women should only take aspirin if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality. Salicylate is excreted in breast milk. (See "Pregnancy," "Labor and Delivery" and "Nursing Mothers" in the "Precautions" section of the Comprehensive Prescribing Information.)

[1]Patients with a pre-existing condition for which aspirin is already indicated. See "Revascularization Procedures" under the "Indications and Usage" and "Clinical Studies" sections in the Comprehensive Prescribing Information.

.....Dosage and Administration.....
General: Each dose should be taken with a full glass of water unless contraindicated. Doses may need to be individualized depending on indication.

Indications	Recommended Daily Dose	Duration of Therapy
Vascular Indications:		
Ischemic Strokes and TIA	50-325 milligrams (mg) daily	Indefinitely
Suspected Acute MI	160-162.5 mg taken as soon as infarction is suspected; then once daily	For 30 days post infarction (after 30 days consider further treatment based on indication for previous MI)
Prevention of Recurrent MI	75-325 mg daily	Indefinitely
Unstable Angina Pectoris	75-325 mg daily	Indefinitely
Chronic Stable Angina Pectoris	75-325 mg daily	Indefinitely
Revascularization Procedures in Select Patients:		
CABG	325 mg daily starting 6 hrs. postprocedure	1 year
PTCA	325 mg 2 hours presurgery Maintenance therapy: 160-325 mg daily	Indefinitely
Carotid Endarterectomy	80 mg daily to 650 mg twice a day started presurgery	Indefinitely
Rheumatologic Disease Indications:		
Rheumatoid Arthritis	Initial dose 3 g daily. Target plasma salicylate levels 150-300 micrograms/milliliter (μg/mL)	As indicated
Juvenile Rheumatoid Arthritis	Initial dose 90-130 mg/kilograms/day. Target plasma salicylate levels 150-300 μg/mL	As indicated
Spondyloarthropathies	Up to 4 grams (g) daily	As indicated
Osteoarthritis	Up to 3 g daily	As indicated
Arthritis and Pleurisy of SLE	Initial dose 3 g daily. Target plasma salicylate levels 150-300 μg/mL	As indicated

CONTRAINDICATIONS
Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drugs and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.
PRECAUTIONS
General
· Renal Failure
· Hepatic Insufficiency
· Sodium Restricted Diets
Laboratory Tests
Drug Interactions:
· Angiotensin Converting Enzyme (ACE) Inhibitors
· Acetazolamide
· Anticoagulant Therapy
· Anticonvulsants
· Beta Blockers
· Diuretics
· Methotrexate
· Nonsteroidal Anti-Inflammatory Drugs (NSAID's)
· Oral Hypoglycemics
· Uricosuric Agents
Carcinogenesis, Mutagenesis, Impairment of Fertility
Pregnancy, Labor and Delivery, Nursing Mothers
Pediatric Use

WARNINGS
· Alcohol Warning
· Coagulation Abnormalities
· Gastrointestinal Side Effects
· Peptic Ulcer Disease
ADVERSE REACTIONS (Most common)
· Gastrointestinal (Abdominal Pain, Ulceration, Bleeding)
· Inhibition of Platelet Aggregation (Bleeding)
· Tinnitus
· Dizziness
· Hearing Loss
To report SERIOUS adverse drug reactions, call (manufacturer) at (phone number) or MEDWATCH at 1-800-FDA-1088
HOW SUPPLIED
(Insert specific information regarding, strength of dosage form, units in which the dosage form is generally available, and information to facilitate identification of the dosage form.) Store in a tight container at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F).

These highlights do not include all the information needed to prescribe aspirin safely and effectively. See aspirin's comprehensive prescribing information.

(b) [Reserved]

Subpart D—Testing Procedures

§ 343.90 Dissolution and drug release testing.

(a) [Reserved]

(b) *Aspirin capsules.* Aspirin capsules must meet the dissolution standard for aspirin capsules as contained in the United States Pharmacopeia (USP) 23 at page 132.

(c) *Aspirin delayed-release capsules and aspirin delayed-release tablets.* Aspirin delayed-release capsules and aspirin delayed-release tablets must meet the drug release standard for aspirin delayed-release capsules and aspirin delayed-release tablets as contained in USP 23 at pages 133 and 136 respectively.

(d) *Aspirin tablets.* Aspirin tablets must meet the dissolution standard for aspirin tablets as contained in USP 23 at page 134.

(e) *Aspirin, alumina, and magnesia tablets.* Aspirin in combination with alumina and magnesia in a tablet dosage form must meet the dissolution standard for aspirin, alumina, and magnesia tablets as contained in USP 23 at page 138.

(f) *Aspirin, alumina, and magnesium oxide tablets.* Aspirin in combination with alumina, and magnesium oxide in a tablet dosage form must meet the dissolution standard for aspirin, alumina, and magnesium tablets as contained in USP 23 at page 139.

(g) *Aspirin effervescent tablets for oral solution.* Aspirin effervescent tablets for oral solution must meet the dissolution standard for aspirin effervescent tablets for oral solution as contained in USP 23 at page 137.

(h) *Buffered aspirin tablets.* Buffered aspirin tablets must meet the dissolution standard for buffered aspirin tablets as contained in USP 23 at page 135.

Dated: OCT 19 1998

October 19, 1998

William B. Schultz

William B. Schultz
Deputy ~~Associate~~ Commissioner for Policy ~~Coordination~~

10-19-98
BJ Beda

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